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(71) Applicant *(for all designated States except US)*: ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).

(72) Inventors; and

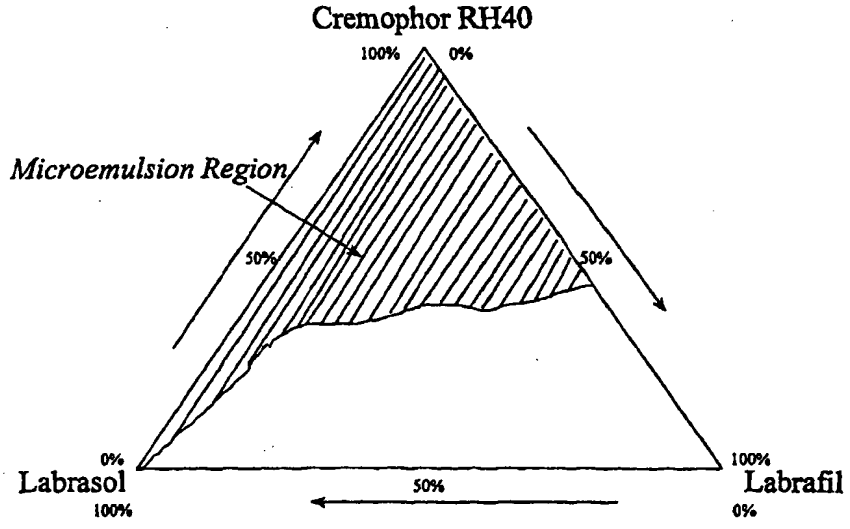
(75) Inventors/Applicants *(for US only)*: RAMTOOLA, Zebunnissa [IE/IE]; 163 Charlemont, Griffith Avenue, Dublin 9 (IE). CLARKE, Nuala, Marie [IE/IE]; 70 Castlefield Court, Clonsilla, Dublin 15 (IE).

(74) Agent: ANNE RYAN & CO.; 60 Northumberland Road, Ballsbridge, Dublin 4 (IE).

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(57) Abstract

Self–emulsifying microemulsion or emulsion preconcentrate pharmaceutical compositions capable of forming an oil–in–water microemulsion or emulsion upon dilution with an aqueous solution are disclosed. The preconcentrate contains a therapeutically effective amount of a poorly water soluble therapeutic agent; a pharmaceutically effective amount of a low HLB oil component; and a surfactant system consisting essentially of at least one surfactant having an HLB of from about 10 to 20 and is substantially free or contains only minor amounts of a hydrophilic solvent system. Microemulsions or emulsions formed by diluting the self–emulsifying preconcentrate with an aqueous solution are also provided.

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Description

Solvent/Cosolvent Free Microemulsion and Emulsion Preconcentrate Drug Delivery Systems

Technical field

The present invention relates to pharmaceutical compositions containing a poorly water soluble therapeutic agent. In particular, the present invention relates to the administration, particularly oral administration to a human, of self-emulsifying microemulsion and emulsion preconcentrate formulations or microemulsions and emulsions which contain a poorly water soluble therapeutic agent, an oil component and a surfactant system. These preconcentrates, microemulsions and emulsions have the advantage of being substantially free of or containing only minor amounts of a hydrophilic solvent system.

Background Art

Certain oil mixtures of lipophilic drugs, such as a cyclosporin, when combined with vegetable oils or other lipidic substances, surface active agents, solvents and other excipients are known to spontaneously produce dispersions of very low mean particle size, such as <200 nm, when mixed with an aqueous medium. These dispersions are known as microemulsions and the oily mixtures that produce the microemulsions are popularly referred to as microemulsion preconcentrates. Upon oral delivery, the microemulsion preconcentrates are thought to produce similar dispersions of very low particle size with gastric and other physiological fluids.

Numerous microemulsion preconcentrate formulations are known, including soft gel formulations, for enhancing the solubilization and oral bioavailability of a poorly water soluble drug compound such as cyclosporin A. Typically, these formulations include an active agent, an oil component, a surfactant to emulsify the formulation and a hydrophilic solvent system containing solvents/co-surfactants to solubilize the active agent.

Typical solvents/co-surfactants include ethanol, polyethylene glycols, propylene carbonate, dimethylisosorbide, Transcutol and/or Glycofurol. Disadvantages of these formulations include stability or precipitation problems caused by migration of volatile hydrophilic solvents or cosolvents (e.g., ethanol can permeate a gelatin shell at normal storage temperatures), stability or precipitation problems caused by hygroscopic solvents or co-surfactants (e.g., propylene glycols, Transcutol, Glycofurol), and toxicity problems caused by addition of certain solvents or co-surfactants (e.g., dimethylisosorbide).

For instance, US 5,603,951 describes a microemulsion concentrate containing cyclosporin as an active ingredient, dimethylisosorbide as a required co-surfactant, a surfactant, and an oil which can be refined fish oil, these components being present in the ratio of 1:1-5:2-10:1-5. The inventors of the '951 patent added dimethylisosorbide, which is a solvent available under the Tradename ARLASOVE®, to the formulation to address the disadvantages listed above for prior solvents/co-surfactants such as ethanol, Transcutol, or Glycofurol. The '951 preconcentrates are formed by dissolving the cyclosporin in the dimethylisosorbide while heating at approximately 60°C followed by addition of the oil component and the surfactant. WO 97/33610 discloses a microemulsion preconcentrate system containing as co-surfactants propylene carbonate or a mixture of propylene carbonate with polyoxyethylene-polyoxypropylene block copolymers. US 5,589,455 discloses a microemulsion preconcentrate system containing the solvent polyethylene glycol. WO 93/20833 discloses a microemulsion preconcentrate system containing a hydrophilic phase, e.g., Transcutol, Glycofurol, 1,2-propylene glycol or ethanol. EP 760237 discloses a microemulsion preconcentrate that includes a phospholipid, preferably lecithin. Phospholipids are disadvantageous in that they are known to have stability issues.

Typically, the oil component of a conventional microemulsion consists of fatty acid mono-, di- or triglycerides from a vegetable oil; medium chain triglycerides and/or mono- or di-glycerides; mixtures of glycerides and polyglycolized glycerides; tocol, tocopherols, and/or tocotrienols; or hydrophobic alcohols. WO 97/22358 discloses a microemulsions system containing tocol, tocopherols, tocotrienols and derivatives along with propylene carbonate or polyethylene glycols. EP 570715 discloses a

microemulsion preconcentrate system containing as a lipophilic phase a mixture of polyglycolized glycerides having a HLB of less than 16. WO 94/25068 discloses a microemulsion preconcentrate system in which hydrophobic alcohols are used in place of the combination of hydrophilic and hydrophobic solvents; while these systems eliminate the need for a hydrophilic solvent system, the hydrophobic alcohols have the disadvantage of tasting bad.

Cyclosporins are an example of a class of drugs that is poorly water soluble. Cyclosporin A (CyA) is a lipophilic cyclic undecapeptide that can be isolated from the fungus *Tolypoclodium inflatum Gams* and which produces calcium dependent, specific and reversible inhibition of transcription of interleukin-2 and several other cytokines, most notably in T helper lymphocytes. Because of its immunosuppressive properties, it is widely used as first line therapy in the prophylaxis and treatment of transplant rejection (e.g., allo- or xeno-transplant rejection such as in patients receiving heart, lung, combined heart-lung, liver, kidney, pancreatic, skin or corneal transplants) and various autoimmune and inflammatory diseases. CyA is used in the treatment of multi-drug resistance syndrome, for example in patients undergoing chemotherapy or following organ transplantations. In patients with severe disease refractory to standard treatment; CyA is an effective therapy in acute ocular Behcet's syndrome; endogenous uveitis; psoriasis; atopic dermatitis; arthritis, particularly rheumatoid arthritis; active Crohn's disease and nephrotic syndrome. Other conditions include arthritis chronica progrediente and arthritis deformans, autoimmune hematological disorders including hemolytic anemia, aplastic anemia, pure red-cell anemia and idiopathic thrombocytopenia, systemic lupus erythematosus, polychondroitis, scleroderma, Wegener granulamtosis, dermatomyositis, chronic active hepatitis, myasthenia gravis, Steven-John syndrome, idiopathic sprue, autoimmune inflammatory bowel disease, e.g., ulcerative colitis, endocrine ophthalmology, Graves disease, sarcoidosis, multiple sclerosis, primary biliary cirrhosis, juvenile diabetes, keratoconjunctivitis sicca and vernal keratoconjunctivitis, interstitial lung fibrosis, psoriatic arthritis, glomerulonephritis, juvenile dermatitis, asthma, tumors, hyperproliferative skin disorders and fungal infections. This drug has also been used to treat patients with moderate or severe aplastic anemia who are ineligible for bone marrow transplantation and those with primary biliary cirrhosis. CyA may be effective

in patients with intractable pyoderma gangrenosum, polymyositis/dermatomyositis or severe, corticosteroid-dependent asthma. CyA is known to have a very specific effect on T-cell proliferation although the precise mechanism remains unclear. A number of non-immunosuppressive analogues of cyclosporin A have been shown to have resistance modifier activity and some are more potent than the parent compound. Nephrotoxicity, hepatotoxicity, hypertension, headache, hypertrichosis, gingival hyperplasia, neurological and gastrointestinal effects, thrombocytopenia and microangiopathic hemolytic anemia, hyperkalemia and hyperuricemia and development of skin and lymphoproliferative malignancies are the most common adverse events in cyclosporin recipients.

Cyclosporins are highly lipophilic, poorly water soluble and, therefore, have been supplied as an olive oil or peanut oil solution for clinical use. However, the bioavailability of cyclosporin from such oily solutions is very low and gives rise to great intersubject variation with reported systemic availability ranging from 4 to 25% (Takada, K. et al, *J. Pharmacobio-Dyn.*, 11:80-7 (1988)). The bioavailability of cyclosporin has been reported to be dependent on food, bile and other interacting factors (*Clin. Pharmacokinetics*, 24:472-95 (1993)). A widely used commercial formulation of CyA, SANDIMMUNE® for oral administration, is a solution of cyclosporin A in vegetable oil derivatives containing some other inactive excipients. Very high inter- and intra-patient and food dependent variability in the bioavailability of CyA has been observed from this formulation. The commercial microemulsion preconcentrate formulation, NEORAL®, has been claimed to provide high bioavailability for CyA with low inter-and intra-patient variability. However, risks of adverse drug reactions have been indicated on switching to Neoral® (*see, e.g., Drug Saf*, 16:366-73 (1996); *Lancet*, 348:205 (1996)).

CyA and fish oils have been administered concurrently to organ transplant patients in various clinical trials. For instance, Andreassen *et al.* (*JAAC*, 29(6):1324-31 (1997) reported effective hypertension prophylaxis in heart transplant patients who were given cyclosporin A and 4g of fish oil. Cyclosporin A-treated and fish oil fed renal transplant recipients had improved renal function following a rejection episode (*Transplantation*, 54:257 (1992)). US 5,118,493 describes the administration of CyA together with an omega-3 fatty acid oil to mediate the nephrotoxic effects of the cyclosporin.

Omega-3 fatty acid oils possess properties that can be used for numerous therapeutic advantages, including treatment of autoimmune and inflammatory diseases such as rheumatoid arthritis, psoriasis, inflammatory bowel diseases such as Crohn's disease and ulcerative colitis; immunosuppressive treatment; hypertension prophylaxis in normal humans and in heart transplant patients; coronary heart disease; hyperlipidemia; hypertriglyceridemia; improvement of renal function and nephrotoxicity reduction. US 4,678,808 describes the use of these oils to treat disorders associated with arachidonic acid metabolites, including autoimmune syndromes, acute and chronic inflammatory diseases, atherosclerosis, stroke, myocardial infarction, deep vein thrombosis, surgery, hyperlipidaemic states, hypertension, enhanced platelet responsiveness, vascular lesions and occlusions, vascular spasm and diabetes. According to US 5,225,441, which describes compositions for treating gingivitis and periodontitis, omega-3 polyunsaturated fatty acids compete with omega-6 polyunsaturated fatty acids as a substrate in the arachidonic acid cascade and can therefore alter the synthesis of prostaglandin and leukotrienes, both of which are powerful mediators of inflammation and immune response. Other uses of omega-3 fatty acid oils are described in US 5,034,415 (diabetes mellitus), US 4,843,095 (rheumatoid arthritis), JP 2253629 (anticancer), US 4,879,312 (enhancing angiogenesis), JP 1290625 (improvement of cerebral function), EP 378,824 (anti-cachexia, cholesterol and triglyceride levels reduction, platelet aggregation inhibition, colon adenocarcinomas growth inhibition), US 5,457,130 (cancer cachexia, malignant tumors, abnormal cAMP levels in adipose tissue, lipolytic activity inhibition) and US 5,436,269 (hepatitis).

It is an object of the present invention to provide a stable, self-emulsifying microemulsion or emulsion preconcentrates and/or a microemulsions or emulsions containing a poorly water soluble therapeutic agent which are capable of enhancing the bioavailability of the therapeutic agent while minimizing the inter- and intra-patient or food variability in the bioavailability of the therapeutic agent. A further object is to provide self-emulsifying preconcentrates or corresponding microemulsions and emulsions having increased therapeutic agent dosing reproducibility compared to conventional formulations. An additional object is to provide self-emulsifying preconcentrates or corresponding microemulsions or emulsions containing a

poorly water soluble therapeutic agent which provide for an enhanced amount of the therapeutic agent in a single dosage unit.

An additional object of this invention is to provide stable self-emulsifying preconcentrates, microemulsions or emulsions containing a poorly water soluble therapeutic agent which are substantially free or contain only minor amounts of a hydrophilic solvent system. In this manner, the disadvantages of prior art systems containing hydrophilic solvent systems, such as stability problems, therapeutic agent precipitation problems and/or toxicity problems, are avoided.

A further object of this invention is to provide a stable self-emulsifying preconcentrate and/or a microemulsion or emulsion in which the poorly water soluble therapeutic agent is substantially soluble in the oil component, thus eliminating or drastically reducing the need for substantial amounts of a hydrophilic solvent system.

It is an additional object of this invention to provide a stable self-emulsifying microemulsion or emulsion preconcentrate and/or a microemulsion or emulsion containing a poorly water soluble therapeutic agent in which the oil component and surfactant system are chosen so as to render the presence of a hydrophilic solvent system unnecessary.

An additional object of this invention is to provide a stable self-emulsifying preconcentrate and/or a microemulsion or emulsion containing a poorly water soluble therapeutic agent and a low HLB oil component that is free or substantially free of a hydrophilic solvent system.

A further object of this invention is to provide a stable self-emulsifying microemulsion or emulsion preconcentrate formulation and/or a microemulsion or emulsion containing a poorly water soluble therapeutic agent which is suitable for formulation into soft or hard capsules for oral administration.

A still further object of this invention is to provide a stable self-emulsifying microemulsion or emulsion preconcentrate soft or hard capsule formulation containing an oil component and a poorly water soluble

therapeutic agent having relatively high amounts of both the oil component and the poorly water soluble therapeutic agent.

Disclosure of Invention

Surprisingly, it has been found that stable, self-emulsifying microemulsion or emulsion preconcentrates comprising a poorly water soluble drug can be formed from a two-component self-emulsifying system containing an oil component having an HLB ≤ 4 and a surfactant system containing one or more surfactants, each surfactant having an HLB from about 10 to 20. This two-component system eliminates or drastically reduces the need for substantial amounts of a hydrophilic solvent system, allowing for formulation of preconcentrates that are substantially free of a hydrophilic solvent system or contain only minor amounts of a hydrophilic solvent system. It was also found that the solubility of a poorly water soluble drug in the low HLB oil component allowed for formulation of preconcentrates containing relatively high quantities of the poorly water soluble drug. The self-emulsifying microemulsion and emulsion preconcentrates according to the present invention take the form of a poorly water soluble therapeutic agent substantially solubilized in a low HLB oil component that is capable of being self-emulsified by the surfactant system when the preconcentrate is diluted with an aqueous medium.

Thus, the present invention provides a self-emulsifying preconcentrate pharmaceutical composition suitable for administration to a mammal, particularly oral administration to a human, and capable of forming an oil-in-water microemulsion or emulsion upon dilution with an aqueous solution, comprising

(a) a therapeutically effective amount of a poorly water soluble therapeutic agent;

(b) a pharmaceutically effective amount of a low HLB oil component; and

(c) a surfactant system consisting essentially of at least one surfactant having an HLB of from about 10 to 20, preferably 13-19, most preferably 15-18;

wherein the composition contains minor amounts or is substantially free of a hydrophilic solvent system. The present invention also provides

microemulsions or emulsions formed by diluting a self-emulsifying preconcentrate with an aqueous solution.

Because the compositions according to this invention are substantially free or contain only minor amounts of a hydrophilic solvent system, the disadvantages of the prior art systems given above are avoided.

Preferred therapeutic agents include a cyclosporin, particularly cyclosporin A, nifedipine or indomethacin and other Class 4 drugs. Preferred low HLB oil components include Labrafil M1944CS; Labrafil M2125CS; and fish oil or other omega-3 fatty acid oils. Preferred omega-3 fatty acid oils include omega-3 free fatty acids, omega-3 fatty acid triglycerides and omega-3 fatty acid ethyl esters, such as EPA, DHA, triglycerides of EPA, triglycerides of DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.

When fish oil is employed in the compositions of the present invention, it is preferable to use fish oil containing at least 50%, preferably at least 70%, more preferably at least 80% omega-3 fatty acid oil to obtain a pharmaceutically effective amount of an omega-3 fatty acid oil in a minimal volume

Brief Description Of Drawings

Figure 1 shows a ternary phase diagram for the placebo system described in Example 3 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of the oil component Labrafil M1944CS (0 to 100%), and the concentration of Cremophor RH40 (0 to 100%) for the placebo system. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor RH40 increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of Labrafil M1944CS increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water;

Figure 2 shows a ternary phase diagram for the 100 mg CyA system described in Example 3 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of Labrafil M1944CS (0 to 100%), and the concentration of Cremophor RH40 (0 to 100%) for compositions containing 100 mg CyA. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor RH40 increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of Labrafil M1944CS increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water;

Figure 3 shows a pseudo-ternary phase diagram for the placebo system described in Example 13 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of the omega-3 fatty acid oil K85TG (0 to 100%), and the concentration of Cremophor RH40:Tween 80 in a 2:1 ratio (0 to 100%) for the placebo system. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor RH40:Tween 80 in a 2:1 ratio increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of K85TG increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water; and

Figure 4 shows a pseudo-ternary phase diagram for the 100 mg CyA system described in Example 13 upon a 1 to 20 dilution of the preconcentrate with water. The diagram plots the relative concentration of Labrasol (0 to 100%), the concentration of the omega-3 fatty acid oil K85TG (0 to 100%), and the concentration of Cremophor RH40:Tween 80 in a 2:1 ratio (0 to 100%) for compositions containing 100 mg CyA. The relative concentration of Labrasol increases from 0% at the lower right hand margin of the diagram to 100% at the lower left corner; the relative concentration of Cremophor

RH40:Tween 80 in a 2:1 ratio increases from 0% at the baseline of the diagram to 100% at the apex; and the relative concentration of K85TG increases from 0% at the apex to 100% at the lower right hand corner of the diagram. The shaded area identifies those compositions having C1, C1/C2 or C2 clarity as the microemulsion region for a 1 to 20 dilution of the preconcentrate with water.

As used herein, the term "low HLB oil component" means a natural or synthetic pharmaceutically acceptable oil or mixture of oils in which the oil or mixture of oils has a hydrophile-lipophile balance (HLB) of ≤ 4. Example low HLB oil components include, but are not limited to, medium and long chain (e.g., >C13) fatty acids and their mono/di/triglycerides or esters having a HLB ≤ 4; unsaturated fatty acids and their mono/di/triglycerides or esters having a HLB$\leq$4; and natural oils such as canola, soybean, corn, olive, sunflower and their mono/di/triglycerides or esters having a HLB$\leq$4; or mixtures thereof. Preferred low HLB oil components include esters, particularly the ethyl esters, of medium and long chain fatty acids. Specific examples of low HLB oil components include, but are not limited to, Labrafil M1944CS; Labrafil M2125CS; ethyl oleate and oleic acid; omega-6 fatty acids and their mono/di/triglycerides or esters such as ethyl esters; and fish oil and other omega-3 fatty acid oils as defined below and mixtures thereof. Examples of oils that are not low HLB oil components include Miglyol 812 (HLB~8-10); Gelucire 44/14 (HLB~14); Gelucire 48/09 (HLB~9); and Labrafil WO 2609 BS (HLB~6).

As used herein, the term "omega-3 fatty acid oil" means a natural or synthetic omega-3 fatty acid, and pharmaceutically acceptable esters, derivatives, precursors or salts thereof and mixtures thereof. Examples of omega-3 fatty acid oils include but are not limited to omega-3 polyunsaturated, long-chain fatty acids such as a eicosapenta-5,8,11,14,17-enoic acid (hereinafter "EPA"), docosahexa-4,7,10,13,16,19-enoic acid (hereinafter "DHA"), and α-linolenic acid; esters of an omega-3 fatty acid with glycerol such as mono-, di- and triglycerides; esters of the omega-3 fatty acid and a primary alcohol such as fatty acid methyl esters and fatty acid ethyl esters; precursors of an omega-3 fatty acid oil, such as EPA and DHA precursor α-linolenic acid; and derivatives such as polyglycolized derivatives or polyoxyethylene derivatives. Preferred omega-3 fatty acid oils are EPA or

DHA, triglycerides thereof, ethyl esters thereof and mixtures thereof. The omega-3 fatty acids or their esters, derivatives, precursors, salts and mixtures thereof can be used either in their pure form or as a component of an oil such as fish oil (otherwise known as marine oil), preferably highly purified fish oil concentrates, or perilla oil or marine microalgae oil. Suitable fish oils are, for example, those types which are recovered in substantial quantities from cold-water fish, such as pilchard oil, menhaden oil, Peruvian fish oil, sardine oil, salmon oil, herring oil, and mackerel oil. Preferably, the fish oil has a high omega-3 fatty acid oil content, such as 50% or higher, more preferably, 70% or higher, most preferably 80% or higher. Examples of suitable omega-3 fatty acid oils include the following oils available from Croda Oleochemicals (England): Incromega TG3525 (35:25 EPA:DHA ratio; triglycerides), Incromega E5015 (50:15 EPA:DHA ratio; ethyl esters) and the following oils available from Pronova Biocare (Sandefjord, Norway): EPAX6000FA, EPAX5000TG, EPAX4510TG, EPAX2050TG, K85TG, K85EE, K80EE and EPAX7010EE (further details listed in Table 1 herein). Preferred mixtures include mixtures of fatty acid ethyl esters and fatty acids; fatty acid ethyl esters and fatty acid triglycerides; fatty acids and fatty acid triglycerides; and fatty acid esters, fatty acid triglycerides and fatty acids such as mixtures containing K85EE and EPAX6000FA; EPAX5000TG and EPAX6000FA; K85EE and EPAX5000TG; and K85EE, EPAX6000FA and EPAX5000TG.

As used herein, the term "therapeutic agent" means a poorly water soluble drug having therapeutic use in a mammal, especially a human, or a combination of such poorly water soluble drugs wherein the drug or combination of drugs is insoluble in water or has an aqueous solubility of less than about 1 part per 1000 parts of water by weight at 20°C.

The therapeutic agent can be selected from a variety of known types of drugs including, but not limited to, analgesics, anti-allergic agents, anti-fungals, anti-inflammatory agents, anti-arrythmic agents, antibiotics, anticoagulants, antidepressants, antidiabetic agents, anti-epilepsy agents, antihypertensive agents, anti-gout agents, anti-malarials, anti-migraine agents, antimuscarinic agents, antineoplastic agents, anti-protozoal agents, anxiolytics, thyroids, anti-thyroids, antivirals, anoretics, bisphosphonates, cardiac inotropic agents, cardiovascular agents, corticosteroids, diuretics, dopaminergic agents, gastrointestinal agents, hemostatics, histamine receptor

antagonists, hypnotics, immunosuppressants, kidney protective agents, lipid regulating agents, muscle relaxants, neuroleptics, neurotropic agents, opioid agonists and antagonists, parasympathomimetics, protease inhibitors, prostglandins, sedatives, sex hormones, stimulants, sympathomimetics, vasodilators and xanthins. The therapeutic agent may comprise a combination of poorly water-soluble drugs. Examples of therapeutic agents include nephrotoxic drugs such as cyclosporins and amphotericin B; indomethacin; nifedipine; cardiotoxic drugs such as amphotericin B and FK506; drugs with immunosuppressive effects or anti-inflammatory drugs such as drugs for treating rheumatology, arthritis, psoriasis, inflammatory bowel disease, Crohn's disease or demyelinating diseases including multiple sclerosis; anti-tumor drugs such as melphalan, chlormethine, extramustinephosphate, uramustine, ifosfamide, mannomustine, trifosfamide, streptozotocin, mitobronitol, methotrexate, fluorouracil, cytarabine, tegafur, idoxide, taxol, paclitaxel, daunomycin, daunorubicin, bleomycin, amphotericin; hyperlipidemia or hypercholestolemia drugs such as fenofibrate; dioplar disease drugs; drugs which increase lipids and/or triglyceride levels; and drugs for treating Alzheimer's disease. Preferred therapeutic agents include Class 4 (low solubility; low permeability) drugs.

When the low HLB oil component is an omega-3 fatty acid oil, compositions according to this invention may also advantageously provide for an additive or synergistic therapeutic effect between the therapeutic agent and the omega-3 fatty acid oil or mediation of at least one negative side effect of the therapeutic agent by the omega-3 fatty acid oil. For instance, in addition to other beneficial co-administration effects, omega-3 fatty acid oil reduces the nephrotoxicity of cyclosporin when co-administered, allowing treatment with higher levels of cyclosporin and producing a greater clinical response at a given dose of cyclosporin.

As used herein, the term "a pharmaceutically effective amount of a low HLB oil component" means an amount effective to solubilize or substantially solubilize a therapeutically effective amount of the poorly water soluble therapeutic agent. As used herein, the term "substantially solubilize" in reference to the solubility of the poorly water soluble therapeutic agent in the low HLB oil component means the poorly water soluble therapeutic agent is soluble in the low HLB oil component oil or has a solubility of more than 1

part per 100 parts of the low HLB oil component by weight at 20°C. Typically the unit dose amount for the low HLB oil component ranges from about 5% to 70% w/w of the microemulsion or emulsion preconcentrate. When the low HLB oil component is an omega-3 fatty acid oil, the amount of omega-3 fatty acid oil in a unit dose of the self-emulsifying microemulsion or emulsion preconcentrate and/or microemulsion or emulsion can be adjusted so that the daily dose of the omega-3 fatty acid oil is from about 1.0 g to about 6.0 g in humans per day, preferably from about 2.0 g to about 5.0 g, most preferably about 2.5 g to about 4.0 g per day. Alternatively, the typical dosage of the omega-3 fatty acid oil ranges from about 14 to 86 mg/kg/day; the typical dosage of a fish oil contains an equivalent amount of omega-3 fatty acid oil.

As used herein, the term "surfactant" means a non-ionic or ionic surfactant having an HLB of from about 10 to 20, more preferably 13-19, most preferably 15-18. Suitable surfactants include but are not limited to polyoxyethylene glycolated natural or hydrogenated vegetable oils; polyoxyethylene sorbitan fatty acid esters; polyoxyethylene fatty acid esters; polyoxyethylene alkyl ethers; polyethylene glycol mono- and di- fatty acid esters; transesterification product of natural vegetable oil triglyceride with polyalkylene polyol; and fatty alcohol ethoxylates. Examples of suitable surfactants include Cremophor-RH40, Cremophor-RH60, Cremophor-EL, Tween-20, Tween-40, Tween-60, Tween-65, Tween-80, Tween-85, Labrasol, Nikkol HCO-50, Nikkol HCO-40, Nikkol HCO-60, Brij 30, Gelucire 44/14, Gycerox 767, Imwitor 742, Imwitor 308, Labrafac Lipophile, Labrafac CM10, Tagat TO, Myrj 52, Myvacet 9-45, and Vitamin E-TPGS.

As used herein, the term "hydrophilic solvent system" means a system comprising a solvent or co-solvent (other than the low HLB oil component) with respect to the poorly water soluble therapeutic agent and/or a co-surfactant having an HLB greater than about 20. Example hydrophilic solvent system components include ethanol, alkylene glycols such as propylene glycol, polyethylene glycol, polyoxypropylene block copolymers, Transcutol, Glycofurol, dimethylisosorbide and mixtures thereof. As used herein, the term "minor amounts" as used in reference to a hydrophilic solvent system means an amount less than about 10% by weight of the components present in the preconcentrate, preferably less than about 5% by weight, most preferably less than the amount of therapeutic agent present in the formulation.

The self-emulsifying microemulsion and emulsion preconcentrate and microemulsion and emulsion formulations according to the present invention may optionally include minor amounts of a hydrophilic solvent system to increase the shelf life or stability of the preconcentrates. Other additives, such as antioxidants or preservatives, may also be present. Examples include tocopherol, tocopherols excipient, ascorbyl palmitate, butylated hydroxyanisol or other antioxidants and preservatives listed in USP XXII, Parmaceutic Ingredients.

The self-emulsifying preconcentrates and the microemulsions and emulsions of the present invention can be adapted for oral administration. Preferred oral dosage forms for the preconcentrates include hard and softgel capsules. Preformed microemulsions and emulsions are preferred oral dosage forms for the microemulsions and emulsions. The formulations according to the present invention can also be administered by other routes of administration, including topical administration or parenteral administration such as i.v. or i.p. administration.

The present invention provides for stable, self-emulsifying microemulsion or emulsion preconcentrates comprising a poorly water soluble drug formed from a two-component self-emulsifying system containing an oil component having an HLB $\leq$ 4 and a surfactant system containing one or more surfactants, each surfactant having an HLB from about 10 to 20. This two-component system eliminates or drastically reduces the need for substantial amounts of a hydrophilic solvent system, allowing for formulation of preconcentrates that are substantially free of a hydrophilic solvent system or contain only minor amounts of a hydrophilic solvent system. Without being limited by any particular theory, it is believed that the combination of a highly lipophilic oil component and a surfactant system containing surfactants having an HLB from about 10 to 20, preferably 13-19, more preferably 15-18 (in the absence of oils or surfactants having an HLB from about 5 to 10) provides stable preconcentrate systems. These particular components allow formulation of preconcentrates that are substantially free of a hydrophilic solvent system or contain only minor amounts of a hydrophilic solvent system. It is believed that the solubilizing properties of the low HLB oil component in combination with surfactants having and HLB from about 10 to 20 allow for formulation of preconcentrates that are substantially free of hydrophilic solvent

system components such as surfactant or co-surfactants having an HLB > 20 or solvents. Enhanced bioavailability for the therapeutic agent from the preconcentrates of the present invention may be due to the absence of these hydrophilic solvent system components that could partition into the aqueous phase upon formation of the microemulsion or emulsion, causing precipitation of the therapeutic agent.

Modes for Carrying Out the Invention

Example 1 – Preparation of Microemulsion/Emulsion Preconcentrates

To make the preconcentrate formulations, a solution containing the poorly water soluble therapeutic agent and the oil component were prepared in appropriate proportions by adding the therapeutic agent in small increments and stirring. The surfactant system was prepared by mixing separately the chosen surfactants in their determined ratios. The oil component/therapeutic agent solution was then combined with the surfactant system solution to form the preconcentrate, such as stirring for approximately 5 minutes with or without heating to 30-40°C until homogeneous. Alternatively, formulations according to the present invention were prepared by simply combining the given amounts of the therapeutic agent, the given amounts of the oil component and the given amounts of the surfactant system with stirring until a homogeneous solution was formed. Alternatively, the therapeutic agent can be added to a mixture of the oil component and the surfactant system and stirred until a homogeneous solution was formed or the surfactant mixture can be prepared, the oil components added to it followed by addition of the drug. To test the behavior of the preconcentrates upon contact with an aqueous system, the preconcentrate was diluted, such as a 1:1, 1:10, 1:20, 1:50 and 1:100 v/v dilution, with an aqueous solution such as water or simulated gastric fluid to simulate conditions in the stomach.

As given in the examples below, a variety of surfactant systems were combined with various oil components at varying ratios and the resulting solutions were diluted with water to determine the ratios that provide suitable microemulsion and emulsion preconcentrate formulations. Clarity of the

resulting solutions was classified as follows: C1 denotes a transparent solution – particle sizing has shown that C1 systems have an average microemulsion droplet sized under 30nm; C2 denotes a translucent solution – droplet size is approximately 50-70nm; C3 denotes a slightly opaque solution – droplet size is in the region of 100nm; and C4 denotes a milky white solution – droplet size is much greater than 100nm. Generally, the self-emulsifying microemulsion systems correspond to the C1 to C2 solutions and the self-emulsifying emulsion systems correspond to the C3 to C4 solutions. A ternary phase diagram that maps the different clarity regions for a particular oil component/surfactant system can be made to visualize the appropriate ratios needed to form a microemulsion preconcentrate or an emulsion preconcentrate formulation.

Oral dosage forms containing the preconcentrates can be prepared. For instance, the therapeutic agent-containing preconcentrate can be transferred to a machine for preparing soft capsules and then encapsulated according to conventional methods for producing soft capsules.

Example 2 – Labrafil M1944CS / Labrasol / Tween 80 /CyA

Samples were prepared according to Example 1 for the oil component, Labrafil M1944CS, and a surfactant system comprising Labrasol and Tween 80 with varying percentages for all three of these components. This system (placebo) resulted in a C1 microemulsion region that contains the oil component up to approximately 20%. Table 1 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water while Table 2 charts 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, and 100 mg of the therapeutic agent cyclosporin A (CyA) per ml of solution were added.

TABLE 1				
Labrafil M1944CS	Labrasol %	Tween 80	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C1
22	65	13	n/a	C4
25	15	60	n/a	C3
27	20	53	n/a	C3
30	56	14	n/a	C4

TABLE 2				
Labrafil M1944CS	Labrasol %	Tween 80	CyA mg/ml	Clarity
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C2
20	38	42	25	C3
5	62	33	50	C3
10	15	75	50	C2
12	45	43	50	C3
20	38	42	50	C3
5	62	33	100	C3
10	15	75	100	C3
12	45	43	100	C3
20	38	42	100	C3

Example 3 – Labrafil M1944CS / Labrasol / Cremophor RH40 / CyA

Samples were prepared according to Example 1 for the oil component, Labrafil M1944CS, and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. This system (placebo) resulted in a C1 or C1/C2 microemulsion region that contains the oil component up to approximately 52%, resulting in an extensive microemulsion region for these preconcentrates as shown in the ternary phase diagram in Fig. 1. This system offers the advantage of good clarity systems at high oil content and thus should offer good solubilization of lipophilic drugs. Table 3 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water while Table 4 charts 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100, 150 and 200 mg of the therapeutic agent CyA per ml of solution were added. C1 or C2 systems were obtained with up to 52% oil at 100 mg/ml CyA loading as shown in the ternary phase diagram of Fig. 2.

TABLE 3				
Labrafil M1944CS	Labrasol %	Cremophor RH40	CyA mg/ml	Clarity
5	62	33	n/a	C1
5	52	43	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C3
20	38	42	n/a	C1
20	27	53	n/a	C1
22	65	13	n/a	C3
27	20	53	n/a	C1
30	56	14	n/a	C3
45	10	45	n/a	C1/C2
48	12	40	n/a	C1/C2
50	11	39	n/a	C1/C2
52	10	37	n/a	C1/C2

TABLE 4				
Labrafil M1944CS	Labrasol %	Cremophor RH40	CyA mg/ml	Clarity
5	62	33	25	C1
10	15	75	25	C1
12	50	38	25	C1
20	43	37	25	C1
27	20	53	25	C1
5	62	33	50	C1
10	15	75	50	C1
12	50	38	50	C1
20	43	37	50	C1
27	20	53	50	C1
5	62	33	100	C3
10	15	75	100	C2
12	50	38	100	C2
20	43	37	100	C1
27	20	53	100	C1
45	10	45	100	C1/C2
48	12	40	100	C1/C2
50	11	39	100	C1/C2
52	10	37	100	C1/C2
5	62	33	150	C4
12	50	38	150	C3
20	43	37	150	C2
27	20	53	150	C2
5	62	33	200	C3
12	50	38	200	C3
20	43	37	200	C3

Example 4 – Labrafil M1944CS / Tween 80 / Cremophor RH40 / CyA

Samples were prepared according to Example 1 for the oil component, Labrafil M1944CS, and a surfactant system comprising Tween 80 and

Cremophor RH40 with varying percentages for all three of these components. This system (placebo) resulted in a C1 or C1/C2 microemulsion region that contains the oil component up to approximately 55%, resulting in an extensive microemulsion region for these preconcentrates. This system offers the advantage of good clarity systems at high oil content and thus should offer good solubilization of lipophilic drugs. Table 5 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water while Table 6 charts 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, and 100 mg of the therapeutic agent CyA per ml of solution were added. C1 or C2 systems were obtained with up to 27% oil at 100 mg/ml CyA loading.

TABLE 5

Labrafil M1944CS	Tween 80	Cremophor RH40	CyA mg/ml	Clarity
5	33	62	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C2
20	38	42	n/a	C1
22	65	13	n/a	C2
27	20	53	n/a	C1
30	56	14	n/a	C2
40	40	20	n/a	C2/C3
40	5	55	n/a	C1/C2
50	25	25	n/a	C1/C2
50	5	45	n/a	C1/C2
55	10	35	n/a	C1/C2
60	5	35	n/a	C2/C3
65	5	30	n/a	C2/C3

TABLE 6				
Labrafil M1944CS	Tween 80	Cremophor RH40	CyA mg/ml	Clarity
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
15	79	6	25	C1
20	38	42	25	C1
22	65	13	25	C2
27	20	53	25	C1
30	56	14	25	C2
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
15	79	6	50	C1
20	38	42	50	C1
22	65	13	50	C2
27	20	53	50	C2
30	56	14	50	C2
5	62	33	100	C2
10	15	75	100	C2
12	45	43	100	C2
15	79	6	100	C3
20	38	42	100	C1
22	65	13	100	C2
27	20	53	100	C2
30	56	14	100	C2

Example 5 – Labrafil M1944CS / Tween 80 / Cremophor RH40 / Labrasol /CyA

Samples were prepared according to Example 1 for the oil component, Labrafil M1944CS, and a surfactant system comprising Cremophor RH40, Tween 80 and Labrasol. The ratio of Cremophor RH40 to Tween 80 was held constant at either 2:1 or 4:1 while the amounts of Labrasol, Labrafil and Cremophor RH40/Tween 80 were varied. At a 2:1 ratio of Cremophor RH40 to Tween 80, the placebo system resulted in a C1 or C1/C2 microemulsion region that contained the oil component up to approximately 45%, resulting in an extensive microemulsion region for these preconcentrates. At 100 mg/ml CyA loading, C1/C2 systems were obtained for points examined between 20% and 50% oil content. At a 4:1 ratio of Cremophor RH 40 to Tween 80, the placebo system results in a C1 or C1/C2 microemulsion region for up to about 45% oil content. Similar clarity systems were obtained with 50mg/ml and 100 mg/ml CyA loading. This system offers the advantage of good clarity

systems at high oil content and thus should offer good solubilization of lipophilic drugs.

The following formulation was prepared and encapsulated in softgel capsules.

Formulation 1

Component	% (wt) of placebo system	wt/capsule
Oil Component: Labrafil M1944CS	50%	550 mg
Surfactant system: Cremophor RH40 and Tween 80 (2:1)	40%	440 mg
Labrasol	10%	110 mg
Therapeutic Agent: Cyclosporin A		100 mg
		1200 mg total

Example 6 – Labrafil M1944CS / Tween 80 / Cremophor RH40 / Labrasol / Therapeutic Agents Indomethacin and Nifedipine

Samples were prepared according to Example 1 for the oil component, Labrafil M1944CS, and a surfactant system comprising Cremophor RH40, Tween 80 and Labrasol. The ratio of Cremophor RH40 to Tween 80 was held constant at either 1:1, 1:2, 2:1 or 4:1 while the amounts of Labrasol, Labrafil and Cremophor RH40/Tween 80 were varied. Table 7 and 8 describe the clarity values upon 1 to 20, 1 to 50 and 1 to 100 dilution in deionized water at 37°C for the placebo systems. An extensive microemulsion region was observed in all cases up to an oil composition of 45% with a 1 to 20 dilution, resulting in either a C1 or a C1/C2 microemulsion. Further increasing the oil content to 50% resulted in a C3 or C2/C3 system at a Cremophor to Tween ratio of 1:2 and 1:1. Increasing the Cremophor to Tween ratio to 2:1 at a 50% oil content resulted in a C2 system. The influence of increasing the dilution factor from 1 in 20 to 1 in 50 and 1 in 100 was evaluated; these larger dilutions may better mimic conditions in the stomach following oral administration of microemulsion preconcentrates. In all cases, increased dilution resulted in the microemulsion remaining at the same clarity or reverting to a more transparent system than the 1 to 20 dilution.

TABLE 7			1:1 Cremophor to Tween			1:2 Cremophor to Tween		
			Appearance of dilutions			Appearance of dilutions		
Labrafil M1944CS	Cremophor: Tween 80	Labrasol	1 in 20	1 in 50	1 in 100	1 in 20	1 in 50	1 in 100
10	80	10	C1	C1	C1	C1	C1	C1
15	50	35	C1	C1	C1	C1	C1	C1
15	35	50	C1	C1	C1	C1	C1	C1
30	50	20	C1	C1	C1	C1	C1	C1
30	40	30	C1/C2	C1	C1	C1	C1	C1
35	60	5	C1/C2	C1	C1	C1/C2	C1	C1
40	30	30	C1/C2	C1/C2	C1	C1/C2	C1/C2	C1/C1
45	45	10	C1/C2	C1/C2	C1	C1/C2	C1/C2	C1/C2
50	20	30	C2/C3	C1	C1/C2	C3	C2/C3	C2/C3

TABLE 8			2:1 Cremophor to Tween			4:1 Cremophor to Tween		
			Appearance of dilutions			Appearance of dilutions		
Labrafil M1944CS	Cremophor: Tween 80	Labrasol	1 in 20	1 in 50	1 in 100	1 in 20	1 in 50	1 in 100
10	80	10	C1	C1	C1	C1	C1	C1
15	50	35	C1	C1	C1	C1	C1	C1
15	35	50	C1	C1	C1	C1	C1	C1
30	50	20	C1/C2	C1	C1	C1	C1	C1
30	40	30	C1/C2	C1/C2	C1	C1/C2	C1/C2	C1
35	60	5	C1/C2	C1/C2	C1	C1/C2	C1	C1
40	30	30	C1/C2	C1/C2	C1/C2	C1/C2	C1/C2	C1
45	45	10	C1/C2	C1/C2	C1/C2	C1/C2	C1	C1
50	20	30	C2	C2	C2	C2/C3	C2	C2

Incorporation of 25 mg/g and 50 mg/g indomethacin in the Labrafil M1944CS, Labrasol and 4:1 Cremophor RH40/Tween 80 system described above yielded the clarity values tabulated in Table 9 (1 in 20 dilutions). 1 in 50 dilutions and 1 in 100 dilutions gave progressively slightly clearer systems.

Incorporation of nifedipine in microemulsion preconcentrates was examined at 25, 50 and 100 mg/g. At Cremophor RH40 to Tween 80 ratios of 1:2, 1:1, 2:1 and 4:1, 25 mg nifedipine was fully soluble in all preconcentrates; 50 mg was solubilized in compositions with oil content up to 35%. Dilution of the nifedipine-loaded preconcentrate at all compositions for the 25 mg/g and at an oil content of up to 35% for the 50 mg/g nifedipine formulations produced an extensive microemulsion region with C1 or C1/C2 clarity being observed. 1 to 50 and 1 to 100 dilutions were also investigated. In all cases, either no change in clarity or a progression to a more transparent C1 system was observed. Table 10 shows the clarity values for 25 mg/g nifedipine in the 1:1, 1:2, 2:1 and 4:1 Cremophor RH40 to Tween systems described above. Sizing of various samples in a Malvern Mastersizer S using a flow-through cell

show that the visually determined C3 values correspond to a mean particle size of less than about 500 nm and C2 values correspond to a mean particle size of less than about 300 nm.

TABLE 9			Indomethacin (25mg/g)	Indomethacin (50mg/g)
			4:1 Cremophor to Tween	4:1 Cremophor to Tween
Labrafil M1944CS	Cremophor: Tween 80	Labrasol	Appearance of 1:20 dilutions	Appearance of 1:20 dilutions
10	80	10	C1	C1
15	50	35	C1	C1
15	35	50	C1	C1
30	50	20	C1	C1
30	40	30	C1	C1
35	60	5	C1	C1
40	30	30	C2	C1/C2
45	45	10	C1/C2	C1
50	20	30	C2	C2

TABLE 10			25 mg/g Nifedipine			
			1:1	1:2	2:1	4:1
Labrafil M1944CS	Cremophor: Tween 80	Labrasol	1 in 20	1 in 20	1 in 20	1 in 20
10	80	10	C1	C1	C1	C1
15	50	35	C1	C1	C1	C1
15	35	50	C1	C1	C1	C1
30	50	20	C1	C1	C1/C2	C1/C2
30	40	30	C1	C1/C2	C1/C2	C1/C2
35	60	5	C1/C2	C1/C2	C1/C2	C1/C2
40	30	30	C2	C2	C2	C2
45	45	10	C1/C2	C2	C1/C2	C1/C2
50	20	30	C2/C3	C3	C2/C3	C2/C3

Example 7 – Solubility of Cyclosporin in Fish Oils at Ambient Temperature

The solubility at ambient temperature for cyclosporin A (CyA) was determined in polyunsaturated omega-3 free fatty acid oil EPAX6000FA , in omega-3 fatty acid glyceride oils EPAX5000TG, EPAX4510TG, EPAX2050TG, and K85TG, in omega-3 fatty acid ethyl ester K85EE and in a mixture of free fatty acid and ethyl ester EPAX6000FA/K85EE (Pronova Biocare, Sandefjord, Norway). The K85TG is a mixed glyceride form obtained by transesterification of K85EE with glycerol giving the resulting blend: K85 monoglyceride: 5-15%; K85 diglyceride: 20-30%; K85 triglyceride: 50-70%

and K85EE remnants: <5%. All of these oils have an HLB ≤ 4. Further details regarding these omega-3 fatty acid oils and the CyA solubilities are given in Table 11.

The solubility of CyA in various oils was found to be variable. A blend of K85EE with EPAX6000FA increased the solubilizing power for CyA greatly compared to either omega-3 fatty acid oil by itself. Furthermore, this CyA solution in a mixture of K85EE and EPAX 6000 remained in the form of a clear solution at low and high temperatures, such as 2-8°C and about 40°C. No precipitation or crystallization occurred upon cooling to about –20°C for more than 24 hours. Thus, these initial findings indicate that CyA microemulsion preconcentrates made with this fish oil blend might have very good thermal stability of over a wide temperature range.

TABLE 11

Fish Oil	Chemical Form	ω-3 content %	EPA %	DHA %	EPA to DHA ratio	Additives mg/g	Solubility mg CyA per g solvent
EPAX6000FA	free fatty acid	55-60	33	22	3:2	Vit A: 1 IU VitD: 1 IU VitE: 3-4.5	≥1000mg/g
EPAX5000TG	glycerides	50	30	20	3:2	VitE: 3.0-4.5	584 mg/g
EPAX4510TG	glycerides	55	45	10	9:2	VitE: min3.0	300 mg/g
EPAX2050TG	glycerides	70	20	50	2:5		459 mg/g
K85TG	glycerides		459	333	1.38:1	VitE: 4.0	>100 mg/g
K85EE	ethyl ester	84	46	38	1.2:1	Vit E: 3.2-4.8	225 mg/g
EPAX7010EE	ethyl ester	82	70	12	5.8:1	Vit E: 2.1-3.2	265 mg/g
K85EE + EPAX6000FA (2:1 w/w)	ethyl ester + free fatty acid	73-76			~3:2		731mg/g

Example 8 – K85EE / Cremophor RH40 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 12 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water while Table 13 charts 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From an analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion preconcentrate formulation formulated according to this system is around 40-45% K85EE.

TABLE 12

K85EE %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	65	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
40	10	50	n/a	C2
50	5	45	n/a	C4
55	10	35	n/a	C4

TABLE 13

K85EE %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	38	42	25	C1
5	62	33	50	C1
10	15	76	50	C1
12	45	43	50	C1
20	38	42	50	C1
5	62	33	100	C3
12	45	43	100	C1
20	38	42	100	C1
5	62	33	150	C4
12	45	43	150	C3
20	38	42	150	C2/C3

Example 9 – K85EE / Tween 80 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol and Tween 80 with varying percentages for all three of these components. Table 14 charts the clarity values upon 1 to 20 dilution with water for this system (placebo) while Table 15 charts the 1 to 20 dilution clarity values for corresponding systems in which 25 and 50 mg of CyA per ml of solution were added.

TABLE 14

KE85EE %	Labrasol %	Tween 80 %	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1/C2
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	55	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
40	5	55	n/a	C2/C3
50	5	45	n/a	C2/C3
53	12	35	n/a	C4

TABLE 15

K85EE %	Labrasol %	Tween 80%	CyA mg/ml	Clarity
5	62	33	25	C2
10	15	75	25	C1
12	45	43	25	C1/C2
20	38	42	25	C2
27	53	20	25	C2
40	5	55	25	C2/C3
50	5	45	25	C4
5	62	33	50	C4
10	15	75	50	C1/C2
12	45	43	50	C2/C3
20	38	42	50	C3
27	53	20	50	C2/C3

Comparison between the K85EE/Cremophor RH40/Labrasol system of Example 8 and the K85EE/Tween 80/Labrasol system of Example 9 shows that while the placebo systems are similar, as cyclosporin is added to the system, the K85EE/Cremophor RH40/Labrasol system provides a larger microemulsion region when plotted on a pseudo-ternary phase diagram.

Example 10 – K85EE / Cremophor RH40 / Tween 80/ Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil K85EE and a surfactant system comprising Labrasol, Tween 80 and Cremophor RH40 (holding the ratio of Cremophor RH40 to Tween 80 at 2:1) with

TABLE 16

K85EE %	Labrasol %	Cremophor RH40:Tween 80 (2:1) %	Ethanol %	CyA mg/ml	Clarity
21.7	0	78.3	n/a	n/a	C1
21.7	12.6	66.7	n/a	n/a	C1
21.7	20.8	67.5	n/a	n/a	C1
31	0	69	n/a	n/a	C1/C2
31	11	68	n/a	n/a	C1/C2
31	18.4	60.6	n/a	n/a	C1/C2
38.8	0	61.2	n/a	n/a	C1/C2
38.8	9.9	51.3	n/a	n/a	C1/C2
38.8	16.2	48	n/a	n/a	C1/C2
42.5	10.5	47	n/a	n/a	C1/C2
44	5	51	n/a	n/a	C2
48.5	0	51.5	n/a	n/a	C2
48.5	8.2	43.3	n/a	n/a	C2
48.5	13.7	37.8	n/a	n/a	C2
21.7	0	78.3	5%	n/a	C1
21.7	12.6	66.7	5%	n/a	C1
21.7	20.8	67.5	5%	n/a	C1
31	0	69	5%	n/a	C1/C2
31	11	68	5%	n/a	C1/C2
31	18.4	60.6	5%	n/a	C1/C2
38.8	0	61.2	5%	n/a	C1/C2
38.8	9.9	51.3	5%	n/a	C1/C2
42.5	10	47.5	5%	n/a	C1/C2
44	5	51	5%	n/a	C1/C2
48.5	0	51.5	5%	n/a	C1/C2
48.5	8.2	43.3	5%	n/a	C2
48.5	13.7	37.8	5%	n/a	C2
52.5	5	42.5	5%	n/a	C2

varying percentages of K85EE, Labrasol and Tween 80/Cremophor RH40. Table 16 charts the 1 to 20 dilution clarity values for this system (placebo) as well as the corresponding system with 5% Ethanol included also. Table 17

charts 1 to 20 dilution clarity values for corresponding systems in which 100 mg of CyA per ml of solution has been added.

Tables 16 and 17 show that inclusion of 5% ethanol compared to the same system without ethanol provides similar microemulsion region sizes for both placebo systems (20% to 50% oil) and the corresponding 100 mg/ml CyA systems.

TABLE 17

K85EE %	Labrasol %	Cremophor RH40:Tween 80 (2:1) %	Ethanol %	CyA mg/ml	Clarity
42.5	10	47.5	n/a	100	C1/C2
44	6	51	n/a	100	C1/C2
46	5	49	n/a	100	C1/C2
46.5	11.5	42	n/a	100	C1/C2
47	0	53	n/a	100	C1/C2
53	8	42	n/a	100	C2/C3
42.5	10	47.5	5%	100	C1/C2
44	6	51	5%	100	C1/C2
46	5	49	5%	100	C1/C2
46.5	11.5	42	5%	100	C2
47	0	53	5%	100	C1/C2
53	8	42	5%	100	C2/C3

Example 11 – EPAX5000TG / Cremophor RH40 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil EPAX5000TG and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 18 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added.

TABLE 18

EPAX5000TG %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C1/C2
22	65	13	n/a	C4
27	20	53	n/a	C1/C2
30	56	14	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	36	42	25	C1
20	27	53	25	C1
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
20	36	42	50	C1
20	27	53	50	C1
5	62	33	100	C1
10	15	75	100	C1
12	45	43	100	C1
20	36	42	100	C1
20	27	53	100	C1
5	62	33	150	C3
10	15	75	150	C1
12	45	43	150	C2
20	36	42	150	C1
20	27	53	150	C1

Example 12 –EPAX6000FA / Cremophor RH40 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil EPAX6000FA and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 19 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion preconcentrate formulation formulated according to this system is around 27% EPAX6000FA.

TABLE 19				
EPAX6000FA %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1
10	15	75	n/a	C1/C2
12	45	43	n/a	C1/C2
15	79	6	n/a	C2
20	38	42	n/a	C2
22	65	13	n/a	C4
27	20	53	n/a	C2
30	56	14	n/a	C4
40	5	55	n/a	C2/C3
50	5	45	n/a	C4
55	10	35	n/a	C4
50	20	30	n/a	C4
40	32	28	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
15	79	6	25	C4
20	38	42	25	C2
22	65	13	25	C4
27	20	53	25	C2
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
15	79	6	50	C4
20	38	42	50	C1
22	65	13	50	C4
27	20	53	50	C2
5	62	33	100	C4
10	15	75	100	C1
12	45	43	100	C1
15	79	6	100	C4
20	38	42	100	C2
22	65	13	100	C4
27	20	53	100	C3
5	62	33	150	C4
10	15	75	150	C2
12	45	43	150	C3
15	79	6	150	C4
20	38	42	150	C3
22	65	13	150	C4
27	20	53	150	C3

Example 13 –K85TG / Cremophor RH40 / Tween 80 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil K85TG and a surfactant system comprising Labrasol, Cremophor RH40 and Tween 80 (with Cremophor RH40 and Tween 80 held at a 2:1 ratio) with varying percentages for the oil, Labrasol and the Cremophor RH40 and Tween 80 mixture. Table 20 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water. A pseudo-ternary phase diagram showing the microemulsion region (C1, C1/C2, and C2 clarity values) for this placebo system upon 1 to 20 dilution is shown in Figure 3.

TABLE 20

K85TG %	Labrasol %	Cremophor RH40: Tween 80 (2:1) %	CyA mg/ml	Clarity
48.5	0	51.5	n/a	C4
48.5	8.2	43.3	n/a	C4
48.5	13.7	37.8	n/a	C4
38.8	0	61.2	n/a	C1/C2
38.8	9.9	51.4	n/a	C3
38.8	16.2	45	n/a	C4
31	0	69	n/a	C2
31	11	58	n/a	C2
31	16.4	50.6	n/a	C4
21.7	0	78.3	n/a	C1/C2
21.7	12.6	65.7	n/a	C1/C2
21.7	20.8	57.5	n/a	C1/C2
40	30	30	n/a	C4
35	20	45	n/a	C2
5	10	85	n/a	C1
5	25	70	n/a	C1
5	50	45	n/a	C1
10	30	60	n/a	C1
10	40	50	n/a	C1/C2
15	10	75	n/a	C1
15	15	70	n/a	C2
15	60	25	n/a	C1/C2
20	25	55	n/a	C1/C2
25	35	40	n/a	C4
25	45	30	n/a	C2
35	20	45	n/a	C2
40	30	30	n/a	C4

Table 21 charts the 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. The pseudo-ternary phase diagram given in Figure 4 shows the

microemulsion region for the system upon 1 to 20 dilution having 100 mg/ml CyA per ml of solution.

TABLE 21

K85TG %	Labrasol %	Cremophor RH40: Tween 80 (2:1) %	CyA mg/ml	Clarity
21.7	0	78.3	100	C1
21.7	12.6	65.7	100	C1
21.7	20.8	57.5	100	C1/C2
31	0	69	100	C1/C2
31	11	58	100	C2
31	16.4	50.6	100	C2/C3
38.8	0	61.2	100	C1/C2
38.8	9.9	51.4	100	C2/C3
38.8	16.2	45	100	C3
48.5	0	51.5	100	C3
48.5	8.2	43.3	100	C3
48.5	13.7	37.8	100	C4

Example 14 –K85TG / Cremophor RH40 / Labrasol

Samples were prepared according to Example 1 for the omega-3 fatty acid oil K85TG and a surfactant system comprising Labrasol and Cremophor RH40 with varying percentages for all three of these components. Table 22 charts the clarity values for this system (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 25, 50, 100 and 150 mg of CyA per ml of solution were added. From an analysis of the placebo system, it appears that the greatest amount of oil possible in a microemulsion preconcentrate formulation formulated according to this system is around 27% K85TG.

The microemulsion region on a ternary phase diagram obtained by plotting the data for the K85EE/Cremophor/Labrasol system provided in this example is similar to that for the corresponding EPAX5000TG system (Example 11) and the EPAX6000FA system (Example 12) over a range of 0 to 150 mg/ml CyA. The corresponding K85EE system (Example 8) appears to form a larger microemulsion region than the K85TG system.

TABLE 22

K85TG %	Labrasol %	Cremophor RH40%	CyA mg/ml	Clarity
5	62	33	n/a	C1/C2
10	15	75	n/a	C1
12	45	43	n/a	C1
15	79	6	n/a	C4
20	38	42	n/a	C2/C3
22	65	13	n/a	C4
27	20	53	n/a	C2
30	56	14	n/a	C4
5	62	33	25	C1
10	15	75	25	C1
12	45	43	25	C1
20	38	42	25	C2
20	27	53	25	C1
5	62	33	50	C1
10	15	75	50	C1
12	45	43	50	C1
20	38	42	50	C2
20	27	53	50	C1
5	62	33	100	C1
10	15	75	100	C1
12	45	43	100	C1
20	38	42	100	C2
20	27	53	100	C1
5	62	33	150	C2
12	45	43	150	C3
20	38	42	150	C3
27	20	53	150	C1

Example 15 – Mixed Fish Oils / Cremophor RH40 / Tween 80 / Labrasol

Samples were prepared according to Example 1 for the systems containing a mixture of K85EE and EPAX6000FA and a surfactant system comprising Labrasol, Tween 80 and Cremophor RH40 with varying percentages as described in Table 23. Table 23 charts the clarity values for these systems (placebo) upon 1 to 20 dilution with water as well as 1 to 20 dilution clarity values for the corresponding systems in which 50 or 100 mg of CyA per ml of solution were added. There was a slight improvement in the clarity of the resulting microemulsions upon the addition of CyA.

TABLE 23

K85EE / EPAX6000FA (2.5:1) %	Cremophor RH40 / Tween 80 (2:1) %	Labrasol %	Clarity (without CyA)	Clarity (with 100 mg CyA)	Clarity (with 50 mg CyA)
21.7	65.7	12.6	C1	C1	C1
31	58	11	C1	C1	C1
38.8	61.2	0	C1/C2	C1/C2	C2
38.8	51.4	9.9	C1/C2	C1/C2	C1/C2
38.8	45	16.2	C1/C2	C1/C2	C1/C2
48.5	51.5	0	C2	C2	C3
48.5	43.3	8.2	C2	C2	C2/C3
48.5	37.8	13.7	C2	C2	C2/C3
50.9	49.1	0	C3	C3	C3
K85EE / EPAX6000FA (5:1) %	**Cremophor RH40 / Tween 80 (4:1) %**	**Labrasol %**	**Clarity (without CyA)**	**Clarity (with 100 mg CyA)**	**Clarity (with 50 mg CyA)**
40	55	5	C2	C1/C2	C1
42.5	52.5	5	C1/C2	C1/C2	C1
45	50	5	C1/C2	C1/C2	C1
47	48	5	C2	C2	C1/C2
K85EE / EPAX6000FA (5:1) %	**Cremophor RH40 / Tween 80 (2:1) %**	**Labrasol %**	**Clarity (without CyA)**	**Clarity (with 100 mg CyA)**	**Clarity (with 50 mg CyA)**
40	55	5	C1/C2	C1/C2	C1/C2
42.5	52.5	5	C2	C1/C2	C1/C2
45	50	5	C2	C1/C2	C2
47	48	5	C2	C2	C2

Example 16 – Formulations

The following formulations according to the present invention were prepared as follows. The given amounts of cyclosporin, the given amounts of the oil containing omega-3 fatty acid oil, and the given amounts of the surfactant system were stirred until a homogeneous solution was formed. The resulting cyclosporin-containing composition was transferred to a machine for preparing soft capsules and then encapsulated according to conventional methods for producing soft capsules. These products were designed for daily administration, for example administration of 3-8 capsules daily, thus providing both a therapeutically effective amount of the therapeutic agent cyclosporin A (300 - 800 mg for Formulations 2 and 3 or 75 - 200 mg cyclosporin A for Formulation 4) and a pharmaceutically effective amount of an omega-3 fatty acid oil (1.03 – 2.74 g EPA + DHA for Formulations 2 and 4 or 1.39 - 3.70 g EPA + DHA for Formulation 3) per day. Formulation 5

contains a mixture of omega-3 fatty acid oils as well as minor amounts of a hydrophilic solvent system. Of course, a daily dose may contain combinations of capsules having differing therapeutic agent and/or omega-3 fatty acid oil amounts such as the capsules of Formulations 2, 3, 4 and 5.

Formulation 2

Component	% (wt) of placebo system	wt/capsule
Oil Component: K85EE	37%	407 mg (343 mg EPA + DHA)
Surfactant system: Cremophor RH40 and Tween 80 (2:1)	53%	583 mg
Labrasol	10%	110 mg
Cyclosporin A		100 mg
		1200 mg total

Formulation 3

Component	% (wt) of placebo system	wt/capsule
Oil Component: K85EE	50%	550 mg (462 mg EPA + DHA)
Surfactant system: Cremophor RH40 and Tween 80 (2:1)	40%	440 mg
Labrasol	10%	110 mg
Cyclosporin A		100 mg
		1200 mg total

Formulation 4

Component	% (wt) of placebo system	wt/capsule
Oil Component: K85EE	37%	407 mg (343 mg EPA + DHA)
Surfactant system: Cremophor RH40 and Tween 80 (2:1)	53%	583 mg
Labrasol	10%	110 mg
Cyclosporin A		25 mg
		1125 mg total

Formulation 5		
Component	**% (wt) of system**	**wt/capsule**
Oil component:		
K85EE and EPAX6000FA (2:1)	37.05%	407.55 mg
Surfactant system:		
Cremophor RH40 and Tween 80 (2:1)	49.05%	539.55 mg
Labrasol	9.35%	102.85 mg
Hydrophilic Solvent System		
Ethanol	4.55%	50.05 mg
Cyclosporin A		100.00 mg
		1200 mg total

Example 17 – Ethyl Oleate / Tween 80 / Cremophor RH40 / Labrasol

Preconcentrate formulations suitable for formulation with a therapeutically effective amount of a poorly water soluble theraputic agent according to this invention and containing ethyl oleate were prepared as detailed in Table 24 (w/w %). The respective amounts of Cremophor RH40 and Tween 80 (2:1) were weighed out initially and allowed to mix at approximately 37°C until homogenous. Following this, Labrasol was added as required and all three surfactants were allowed combine until they had formed a clear homogenous mix. The appropriate oil component was added to the mixture of surfactants and allowed to mix. Finally, ethanol was included if present.

Microemulsions were formed by diluting 1:20 with deionised water and microemulsion formation was assessed. The average particle size was measured by photon correlation spectroscopy (C3 and C4 formulations diluted up to 1:400 as necessary) as shown in Table 24.

TABLE 24

Ethyl Oleate	Labrasol	Cremophor: Tween (2:1)	EtOH	Preconcentrate Appearance	Microemulsion Appearance	Droplet Size (Z ave)
30	5	60	5	Clear	C1	27.5 nm
30	10	55	5	Clear	C1	26.6 nm
35	15	45	5	Clear	C1/C2	32.7 nm
37	5	53	5	Clear	C1/C2	37.0 nm
40	5	50	5	Clear	C1/C2	39.3 nm
40	10	45	5	Clear	C1/C2	39.6 nm
45	10	40	5	Clear	C2	62.3 nm
50	5	40	5	Clear	C2/C3	74.5 nm
50	10	35	5	Hazy	C4	113.3 nm
55	5	35	5	Hazy	C4	135.8 nm
30	5	65	0	Clear	C1	26.6 nm
30	10	60	0	Clear	C1	26.0 nm
35	15	50	0	Clear	C1/C2	31.1 nm
37	5	58	0	Clear	C1/C2	34.9 nm
40	5	55	0	Clear	C1/C2	37.8 nm
40	10	50	0	Clear	C1/C2	37.9 nm
45	10	45	0	Clear	C2	50.6 nm
50	5	45	0	Clear	C2/C3	72.0 nm
50	10	40	0	Clear, on standing	C2	70.3 nm
55	5	40	0	Clear, on standing	C3	95.5 nm

In formulations containing 5% ethanol it was observed that at 30% ethyl oleate, clear preconcentrates and microemulsions of droplet size under 30nm were produced at both Labrasol concentrations of 5 and 10%. When the ethyl oleate content was increased from 30% to 40%, preconcentrates still remained clear. However microemulsion droplet size had increased by 10 – 15nm, to approximately 40nm. At 45% ethyl oleate, microemulsion clarity of C2 was observed with a droplet size of 62.3nm. Further increase in ethyl oleate composition to 50% gave a decrease in microemulsion clarity to a C2/C3 system. At this concentration of ethyl oleate, Labrasol composition was found to influence droplet size, which increased to 74.5nm and 113.3nm for a Labrasol concentration of 5% and 10% respectively. At 55% ethyl oleate and 5% Labrasol, a hazy preconcentrate with a C4 microemulsion of droplet size 135.8nm was produced.

In formulations with no ethanol, it was observed that for preconcentrates containing 30% ethyl oleate and Labrasol, at both 5% and 10% concentrations, clear preconcentrates and microemulsions of droplet size approximately equal to 26nm were produced. When the ethyl oleate

content was increased to 35%, 37% and 40%, together with a Labrasol concentration of 15%, 5% and 5% respectively, preconcentrates still remained clear with microemulsion droplet size under 38nm. Increasing Labrasol content to 10% with 40% ethyl oleate produced a droplet size of 37.9nm. At 45% ethyl oleate concentration, in conjunction with 10% Labrasol, microemulsion clarity of C2 and droplet size of 50.6nm was produced. When 50% ethyl oleate was formulated with 5% and 10% Labrasol, microemulsion clarity decreased to C2/C3 in both cases, while droplet size increased to 72.0nm 70.3nm respectively. At 55% ethyl oleate and 5% Labrasol, the preconcentrate appeared hazy after formulation, but went clear on standing. A C3 microemulsion resulted from dilution of this preconcentrate, with a droplet size of 95.5nm.

Thus, below an ethyl oleate concentration of 40%, Labrasol concentration (up to 10%) has no significant effect on microemulsion droplet size. However, above an ethyl oleate concentration of 40%, Labrasol concentration (at 5% and 10%) has a significant effect on microemulsion droplet size. The use of ethyl oleate, up to 40% concentration, in conjunction with 5% and 10% Labrasol produces clear preconcentrates, and subsequently microemulsions of droplet size less than 40nm. Increasing ethyl oleate concentration above 40%, regardless of Labrasol concentration, produced microemulsions of droplet size larger than 40nm. At the higher oil content of 50 and 55%, omission of ethanol in the formulation was found to reduce microemulsion droplet size.

Example 18 – Oleic Acid / Tween 80 / Cremophor RH40 / Labrasol

Similar to Example 17 above, preconcentrate formulations suitable for formulation with a therapeutically effective amount of a poorly water soluble theraputic agent according to this invention and containing oleic acid were prepared and assessed as detailed in Table 25 (w/w %).

TABLE 25

Oleic Acid	Labrasol	Cremophor: Tween (2:1)	EtOH	Preconcentrate Appearance	Microemulsion Appearance	Droplet Size (Z ave)
15	5	75	5	Clear	C4	194.0 nm
30	5	60	5	Clear	C4	211.3 nm
37	5	53	5	Clear	C4	*
50	5	40	5	Clear	C4	*
37	5	58	0	Clear	C4	*
50	5	45	0	Clear	C4	*

* These microemulsions were unsizeable by PCS, even at 1:800 dilution of the respective preconcentrates.

The preconcentrates produced were clear, one-phased systems on formulation, and showed no sign of phase separation or streaking after being left to stand for 24hrs. Dilution (1 in 20) of the 15% and 30% oleic acid preconcentrates gave a clarity of C4 and an average particle size of 194.0nm and 211.3nm respectively. Concentrations of 37% and 50% oleic acid were used to make up preconcentrates, in conjunction with 5% Labrasol, 5% ethanol and Cremophor:Tween (2:1) as required. Both formulations gave one phase, clear, pale yellow preconcentrates. Subsequent emulsions produced (at 1:20 dilution) were in both cases of C4 clarity and were unsizeable by the Zetasizer, even at a 1:800 dilution. Finally 37% and 50% oleic acid preconcentrates, with no ethanol, were formulated. Again, both formulations gave one phase, non-streaking, pale yellow preconcentrates. The 37% formulation produced a C4 emulsion on 1:20 dilution, and was not sizeable by PCS, even at a 1:800 dilution. The 50% formulation produced a C4 emulsion on 1:20 dilution and again was not sizeable, even on 1:800 dilution.

The present invention is not to be limited in scope by the specific embodiments described herein. Indeed, various modifications of the invention in addition to those described herein will become apparent to those skilled in the art from the foregoing description and accompanying figures. Such modifications are intended to fall within the scope of the appended claims.

CLAIMS: -

1. A self-emulsifying preconcentrate pharmaceutical composition capable of forming an oil-in-water microemulsion or emulsion upon dilution with an aqueous solution, comprising:
 a) a therapeutically effective amount of a poorly water soluble therapeutic agent;
 b) a pharmaceutically effective amount of a low HLB oil component; and
 c) a surfactant system consisting essentially of at least one surfactant having an HLB of from about 10 to 20;
 wherein the composition contains minor amounts or is substantially free of a hydrophilic solvent system.

2. A composition according to Claim 1, wherein the composition is a microemulsion preconcentrate.

3. A composition according to Claim 1, wherein the composition is an emulsion preconcentrate.

4. A composition according to any preceding claim, wherein the composition is adapted for oral administration.

5. A composition according to any preceding claim, wherein the low HLB oil component is present in an amount ranging from 5 to 70% by weight.

6. A composition according to any preceding claim, wherein the therapeutic agent is selected from a cyclosporin, nifedipine and indomethacin.

7. A composition according to any preceding claim, wherein the low HLB oil component comprises a low HLB oil component selected from Labrafil M1944CS; Labrafil M2125CS; oleic acid; ethyl oleate; EPA, salts of EPA, DHA, salts of DHA, triglycerides of EPA, triglycerides of DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.

8. A composition according to any one of Claims 1-6, wherein the low HLB oil component comprises a fish oil or a mixture of fish oils.

9. A composition according to any one of Claims 1-6, wherein the low HLB oil component comprises medium or long-chain fatty acid triglycerides.

10. A composition according to any one of Claims 1-6, wherein the low HLB oil component comprises medium or long-chain fatty acid ethyl esters.

11. A composition according to any preceding claim, wherein the therapeutic agent is selected from an analgesic, anti-allergic agent, anti-fungal, anti-inflammatory agent, anti-arrythmic agent, antibiotic, anticoagulant, antidepressant, antidiabetic agent, anti-epilepsy agent, antihypertensive agent, anti-gout agent, anti-malarial, anti-migraine agent, antimuscarinic agent, antineoplastic agent, anti-protozoal agent, anxiolytic, thyroid, anti-thyroid, antiviral, anoretic, bisphosphonate, cardiac inotropic agent, cardiovascular agent, corticosteroid, diuretic, dopaminergic agent, gastrointestinal agent, hemostatic, histamin receptor antagonist, hypnotic, immunosuppressant, kidney protective agent, lipid regulating agent, muscle relaxant, neuroleptic, neurotropic agent, opioid agonist and antagonist, parasympathomimetic, protease inhibitor, prostglandin, sedative, sex hormone, stimulant, sympathomimetic, vasodilator and xanthin or mixtures thereof.

12. A composition according to any one of Claims 1-3, wherein the composition is adapted for topical administration.

13. A composition according to any one of Claims 1-3, wherein the composition is adapted for parenteral administration.

14. A microemulsion or emulsion pharmaceutical composition comprising the self-emulsifying preconcentrate according to any one of Claims 1-13 diluted with an aqueous solution.

15. A composition according to Claim 14, wherein the composition is a microemulsion.

16. A composition according to Claim 14, wherein the composition is an emulsion.

17. A composition according to any one of Claims 14-16, wherein the composition is adapted for oral administration.

18. A composition according to any one of Claims 14-17, wherein the therapeutic agent is selected from a cyclosporin, nifedipine and indomethacin.

19. A composition according to any one of Claims 14-18, wherein the low HLB oil component comprises a low HLB oil component selected from Labrafil M1944CS; Labrafil M2125CS; oleic acid; ethyl oleate; EPA, salts of EPA, DHA, salts of DHA, triglycerides of EPA, triglycerides of DHA, ethyl esters of EPA, ethyl esters of DHA and mixtures thereof.

20. A composition according to any one of Claims 14-18, wherein the low HLB oil component comprises a fish oil or a mixture of fish oils.

21. A composition according to any one of Claims 14-20, wherein the therapeutic agent is selected from an analgesic, anti-allergic agent, anti-fungal, anti-inflammatory agent, anti-arrythmic agent, antibiotic, anticoagulant, antidepressant, antidiabetic agent, anti-epilepsy agent, antihypertensive agent, anti-gout agent, anti-malarial, anti-migraine agent, antimuscarinic agent, antineoplastic agent, anti-protozoal agent, anxiolytic, thyroid, anti-thyroid, antiviral, anoretic, bisphosphonate, cardiac inotropic agent, cardiovascular agent, corticosteroid, diuretic, dopaminergic agent, gastrointestinal agent, hemostatic, histamine receptor antagonist, hypnotic, immunosuppressant, kidney protective agent, lipid regulating agent, muscle relaxant, neuroleptic, neurotropic agent, opioid agonist and antagonist, parasympathomimetic, protease inhibitor, prostglandin, sedative, sex hormone, stimulant, sympathomimetic, vasodilator and xanthin or mixtures thereof.

22. A composition according to any one of Claims 14-19 and 21, wherein the low HLB oil component comprises medium or long-chain fatty acid triglycerides.

23. A composition according to any one of Claims 14-19 and 21, wherein the low HLB oil component comprises medium or long-chain fatty acid ethyl esters.

24. A composition according to any one of Claims 14-23, wherein the composition is adapted for topical administration.

25. A composition according to any one of Claims 14-23, wherein the composition is adapted for parenteral administration.

26. A composition according to any one of Claims 14-25, wherein the amount of aqueous solution to preconcentrate is 1:1 or greater.

27. A self-emulsifying preconcentrate pharmaceutical composition according to Claim 1, substantially as hereinbefore described and exemplified.

28. A microemulsion or emulsion pharmaceutical composition according to Claim 14, substantially as hereinbefore described and exemplified.

Fig. 1

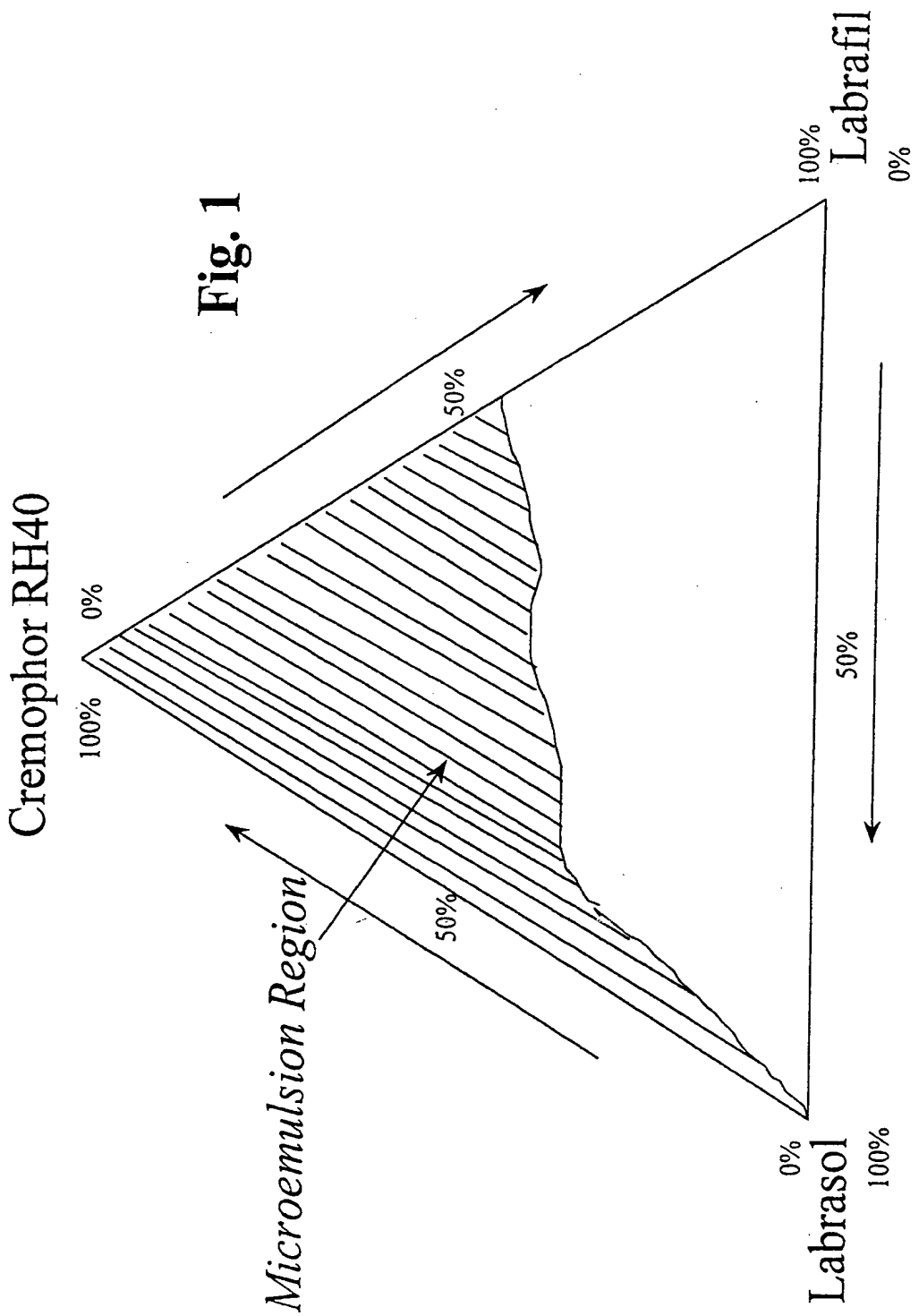

Cremophor RH40
0%
100%
Labrafil
100%
0%
Labrasol
0%
100%
50%
50%
50%
Microemulsion Region

Fig. 2

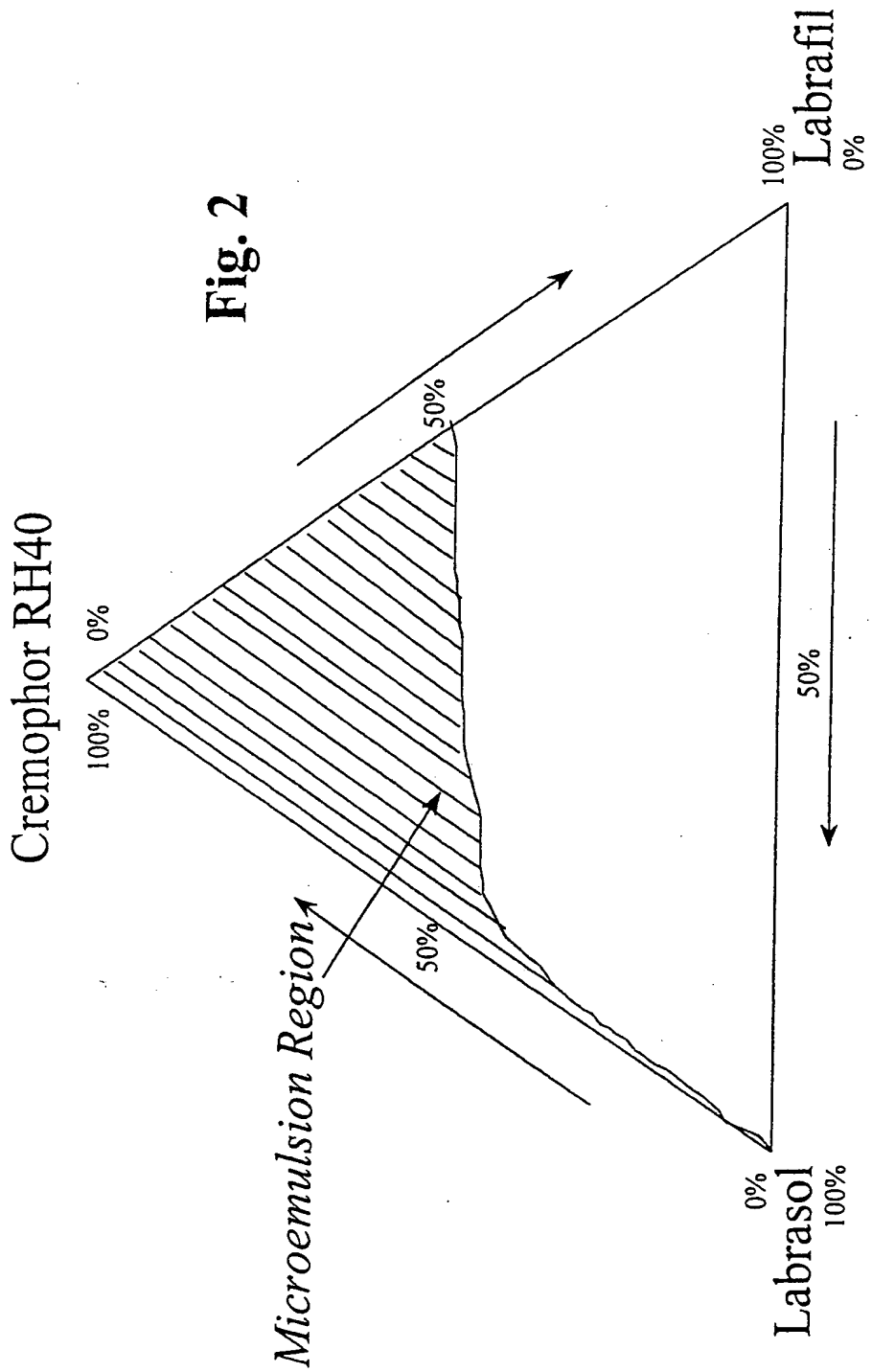

Cremophor RH40
0%
100%
100%
Labrafil
0%
50%
50%
50%
Microemulsion Region
0%
100%
Labrasol

Fig. 3

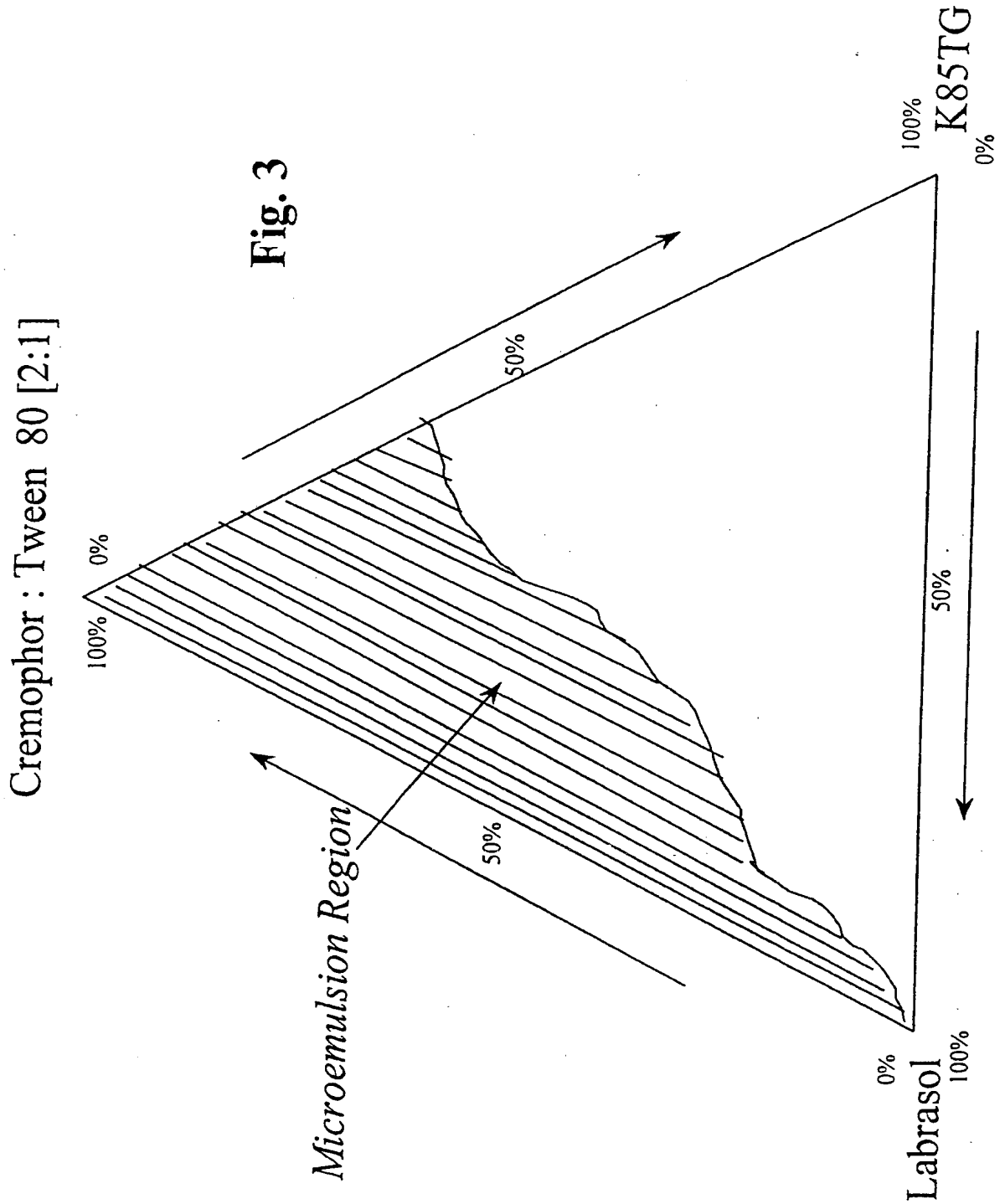
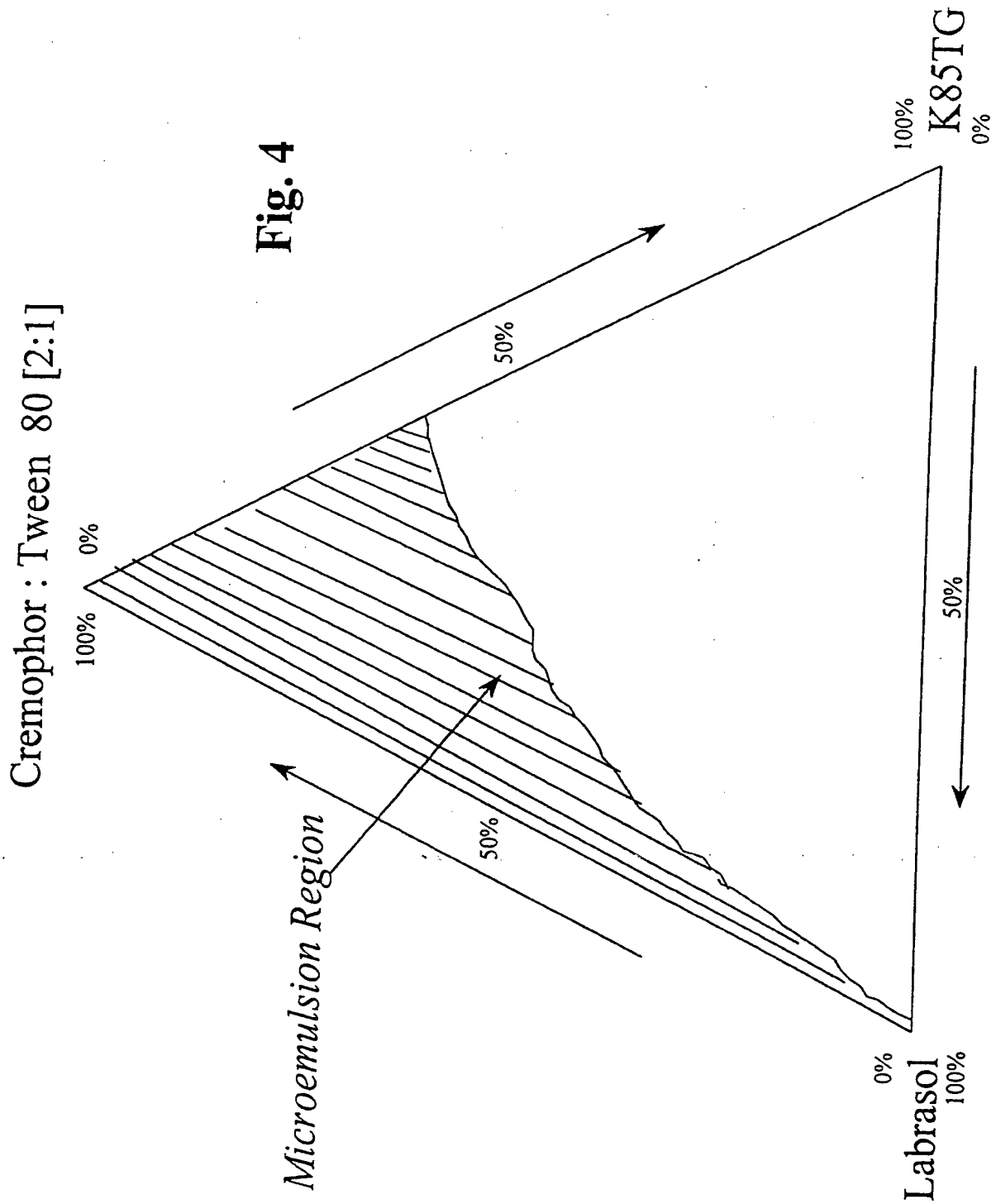

Cremophor : Tween 80 [2:1]
100%
0%
50%
50%
Microemulsion Region
100%
K85TG
0%
50%
0%
Labrasol
100%

Fig. 4


Cremophor : Tween 80 [2:1]
100%
0%
K85TG
100%
0%
Labrasol
0%
100%
50%
50%
50%
Microemulsion Region

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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(71) Applicant *(for all designated States except US)*: ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: RAMTOOLA, Zebunnissa [IE/IE]; 163 Charlemont, Griffith Avenue, Dublin 9 (IE). CLARKE, Nuala, Marie [IE/IE]; 70 Castlefield Court, Clonsilla, Dublin 15 (IE).

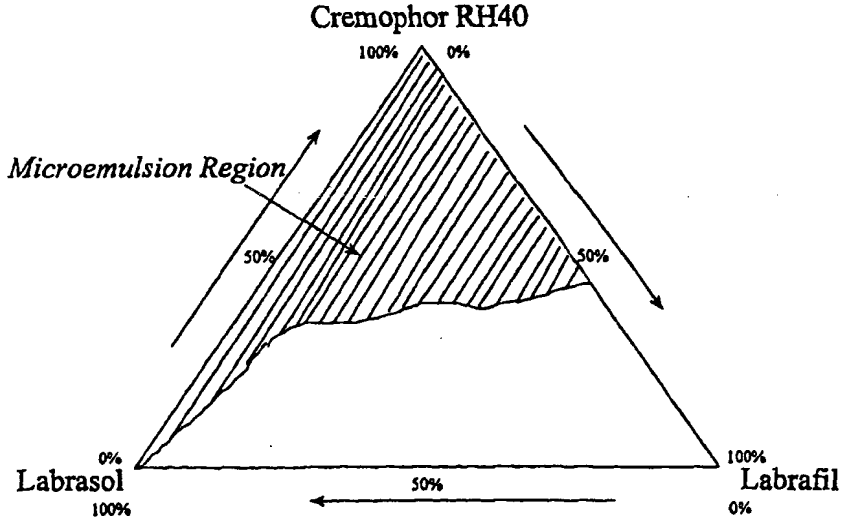
(74) Agent: ANNE RYAN & CO.; 60 Northumberland Road, Ballsbridge, Dublin 4 (IE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(57) Abstract

Self–emulsifying microemulsion or emulsion preconcentrate pharmaceutical compositions capable of forming an oil–in–water microemulsion or emulsion upon dilution with an aqueous solution are disclosed. The preconcentrate contains a therapeutically effective amount of a poorly water soluble therapeutic agent; a pharmaceutically effective amount of a low HLB oil component; and a surfactant system consisting essentially of at least one surfactant having an HLB of from about 10 to 20 and is substantially free or contains only minor amounts of a hydrophilic solvent system. Microemulsions or emulsions formed by diluting the self–emulsifying preconcentrate with an aqueous solution are also provided.

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INTERNATIONAL SEARCH REPORT

Interr. nal Application No
PCT/IE 99/00031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 29316 A (MISHRA AWADHESH K ;MOUSSA ISKANDAR (CA); CLARKE NUALA M (IE); CYCL) 17 June 1999 (1999-06-17) page 6, line 14 -page 7, line 14 page 16 -page 18; examples 3,4 ---	1-3,27
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X	EP 0 650 721 A (HANMI PHARM IND CO LTD) 3 May 1995 (1995-05-03) page 3, line 10 - line 20 page 4, line 7 - line 28 page 5; example 1 page 6 -page 7; example 3 ---	1,2,4-9, 11,13
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2000	19 01 2000

Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

Interr. ..al Application No
PCT/IE 99/00031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 08983 A (GATTEFOSSE ETS SA ;FARAH NABIL (FR); DENIS JOEL (FR)) 6 April 1995 (1995-04-06) page 1, line 5 - line 18 page 9 -page 10; example 1 page 12 -page 13; examples 6,8	1,2,4-7, 9,11-15, 17-19, 21-28
X	EP 0 760 237 A (CIPLA LIMITED) 5 March 1997 (1997-03-05) cited in the application page 2, line 39 - line 57 page 5; examples 1-3	1,2,4-6, 9,11-13
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X	WO 97 36610 A (CHONG KUN DANG CORP) 9 October 1997 (1997-10-09) cited in the application page 1, line 5 - line 16 page 10, line 13 -page 11, line 2 page 16 -page 19; examples 1,2,5	1,2,4-7, 9,11-15, 17-19, 21,22, 24,25, 27,28
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INTERNATIONAL SEARCH REPORT

Interi nal Application No
PCT/IE 99/00031

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication,where appropriate, of the relevant passages	Relevant to claim No.
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X	WO 95 25504 A (BURNSIDE BETH A ;MCCARTY JOHN A (US); PHARMAVENE INC (US); RUDNIC) 28 September 1995 (1995-09-28) page 3, paragraph 3 page 15, paragraph 4 page 16 -page 18; examples 1-7	14-18, 21,22, 24-26
X	CRAIG D Q M ET AL: "A COMPARISON OF THE SELF-EMULSIFYING PROPERTIES OF POLYGLYCOLYSED GLYCERIDE OILS" PHARMACEUTICAL SCIENCES,GB,LONDON, vol. 1, no. 12, page 559-561 XP002053051 ISSN: 1356-6881 the whole document	1-5,7, 12-17, 19,24, 25,27,28
X	SHAH N H ET AL: "SELF-EMULSIFYING DRUG DELIVERY SYSTEMS (SEDDS) WITH POLYGLYCOLYZED GLYCERIDES FOR IMPROVING IN VITRO DISSOLUTION AND ORAL ABSORPTION OF LIPOPHILIC DRUGS" INTERNATIONAL JOURNAL OF PHARMACEUTICS,NL,AMSTERDAM, vol. 106, no. 1, page 15-23 XP000561369 ISSN: 0378-5173 page 21; figure 11	1,3-5,7, 9,12-14, 16,17, 19,22, 24,25, 27,28

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 99/00031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. [X] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

☐ The additional search fees were accompanied by the applicant's protest.

[X] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

International Application No. PCT/IE 99/00031

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partially), 2, 4-14 (partially), 15, 17-28 (partially)

 Preconcentrate of microemulsion and the corresponding microemulsion obtained by addition of an aquous solution

2. Claims: 1 (partially), 3, 4-14 (partially), 16, 17-28 (partially)

 Preconcentrate of an emulsion and the corresponding emulsion obtained with an aquous solution

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat.al Application No
PCT/IE 99/00031

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Information on patent family members

Interr. ...nal Application No
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60/084,518 7 May 1998 (07.05.98) US

(71) Applicant *(for all designated States except US)*: ELAN CORPORATION, PLC [IE/IE]; Lincoln House, Lincoln Place, Dublin 2 (IE).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: RAMTOOLA, Zebunnissa [IE/IE]; 163 Charlemont, Griffith Avenue, Dublin 9 (IE). CLARKE, Nuala, Marie [IE/IE]; 70 Castlefield Court, Clonsilla, Dublin 15 (IE).

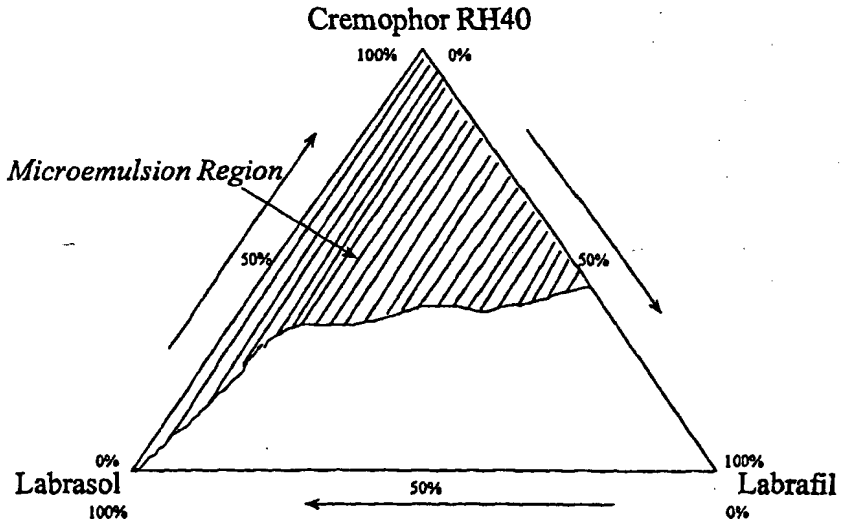
(74) Agent: ANNE RYAN & CO.; 60 Northumberland Road, Ballsbridge, Dublin 4 (IE).

(81) Designated States: AE, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZA, ZW, ARIPO patent (GH, GM, KE, LS, MW, SD, SL, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

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(54) Title: SOLVENT/COSOLVENT FREE MICROEMULSION AND EMULSION PRECONCENTRATE DRUG DELIVERY SYSTEMS



(57) Abstract

Self–emulsifying microemulsion or emulsion preconcentrate pharmaceutical compositions capable of forming an oil–in–water microemulsion or emulsion upon dilution with an aqueous solution are disclosed. The preconcentrate contains a therapeutically effective amount of a poorly water soluble therapeutic agent; a pharmaceutically effective amount of a low HLB oil component; and a surfactant system consisting essentially of at least one surfactant having an HLB of from about 10 to 20 and is substantially free or contains only minor amounts of a hydrophilic solvent system. Microemulsions or emulsions formed by diluting the self–emulsifying preconcentrate with an aqueous solution are also provided.

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INTERNATIONAL SEARCH REPORT

Interr. ...al Application No
PCT/IE 99/00031

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 A61K9/107 A61K9/48

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
E	WO 99 29316 A (MISHRA AWADHESH K ;MOUSSA ISKANDAR (CA); CLARKE NUALA M (IE); CYCL) 17 June 1999 (1999-06-17) page 6, line 14 -page 7, line 14 page 16 -page 18; examples 3,4 ---	1-3,27
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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
12 January 2000	19 01 2000

Name and mailing address of the ISA	Authorized officer
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Interr. ...al Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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X	WO 95 08983 A (GATTEFOSSE ETS SA ;FARAH NABIL (FR); DENIS JOEL (FR)) 6 April 1995 (1995-04-06) page 1, line 5 - line 18 page 9 -page 10; example 1 page 12 -page 13; examples 6,8	1,2,4-7, 9,11-15, 17-19, 21-28
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Interi nal Application No
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/IE 99/00031

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

see additional sheet

1. ☒ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

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☐ The additional search fees were accompanied by the applicant's protest.

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INTERNATIONAL SEARCH REPORT

International Application No. PCT/IE 99/00031

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. Claims: 1 (partially), 2, 4-14 (partially), 15, 17-28 (partially)

 Preconcentrate of microemulsion and the corresponding microemulsion obtained by addition of an aquous solution

2. Claims: 1 (partially), 3, 4-14 (partially), 16, 17-28 (partially)

 Preconcentrate of an emulsion and the corresponding emulsion obtained with an aquous solution

INTERNATIONAL SEARCH REPORT

Information on patent family members

Internat.al Application No
PCT/IE 99/00031

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